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ADAMS & ADAMS,
Allied Building,
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A & A Ref: 57058

Patents Form No. 1A.

REPUBLIC OF SOUTH AFRICA

THE PATENTS ACT, 1952, AS AMENDED.

APPLICATION FOR A PATENT UNDER INTERNATIONAL ARRANGEMENTS (WITH AUTHORISATION OF AGENT)

change I.t.o. request 7/10/70.

Application No. 68/1014

FOR OFFICIAL USE ONLY

Full Name(s) of Applicant(s): SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing according to the laws of the Federal Republic of Germany,

Address(es) of applicant(s): 170-172 Müllerstrasse, 1 Berlin 65, Germany and Waldshaase 14, D 4619 Bergkamen, Germany

Full name(s) of inventor(s): KARL-HEINZ KIMBEL

I/We do hereby declare that I am/we are in possession of an invention the title of which is

"CONTRACEPTIVE PREPARATIONS"

I am/We are the assignee(s)~~/legal representative(s)~~ of the inventor(s). Application(s) for protection for the invention has/have been made in the following country/countries and on the following official dates i.e.:—

1. (country) Germany	(date) 28th February, 1967	(number) Sch 40 314 IVa/30
2. (country)	(date)	(number)
3. (country)	(date)	(number)

The said application or each of the said applications was the first application in a convention country in respect of the relevant invention by me/us or by any person from whom I/we derive title. To the best of my/our knowledge and belief there is no lawful ground for objection to the grant of a patent to me/us on this application. I/We pray that a patent be granted to me/us for the invention in priority over other applicants and that such patent shall have the official date of the first application in a convention country i.e. 28th February, 1967

~~I/We hereby appoint the partners and qualified staff of the firm of ADAMS & ADAMS, jointly and severally, to act for me/us in all matters relating to this application and any letters patent granted thereon~~

Dated this 15th day of February, 196 8

Address for service:
C/o ADAMS & ADAMS,
ALLIED BUILDING,
PRETORIA.

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PATENT ATTORNEY.

Table of Classification	
Class	Sub-class

Signature of Applicant/s and Capacity

PATENTS

FORM NO. 3

A. & A. Ref. No. 57058

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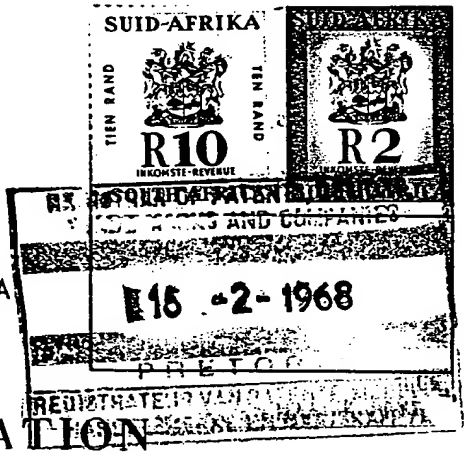

REPUBLIC OF SOUTH AFRICA

The Patents Act, 1952

COMPLETE SPECIFICATION

68/1014

Here insert (in full) name, address of applicant(s) as in application form.

(a) SCHERING AKTIENGESELLSCHAFT, a Body Corporate organized and existing according to the laws of the Federal Republic of Germany of 170-172 Müllerstrasse, 1 Berlin 65, Germany, and Waldshaasse 14, D 4619 Bergkamen, Germany.

Here insert title (verbally agreeing with that in the application form.)

(b) "CONTRACEPTIVE PREPARATIONS"

I/WE do hereby declare this invention, the manner in which and the method by which it is to be performed, to be particularly described and ascertained in and by the following statement:-

The present invention is concerned with contraceptive preparations.

Hormonal methods of contraception have been known, for example the oral administration of Enovid, Ovulen and Anovlar (Registered Trade Marks) and similar combinations of oestrogenic and gestagenic active principles. Experiments have also been made with corresponding preparations for administration by injection in which the active components provide a depot from which they are slowly liberated.

The disadvantage of the latter method is, in particular, the unpredictability of onset, the duration and the extent of withdrawal bleeding. The published experiments, in which a prolonged-action oestrogen and a prolonged-action gestagen are administered together in the first week of the menstrual cycle by injection to suppress ovulation by means of an adequately high oestrogen and progesterone level, have shown that the reduction of the progesterone concentration in the body is not uniform enough to enable the onset of withdrawal bleeding to be predicted within a span of a few days, which is generally possible in the case of natural menstruation.

The disadvantage of oral administration lies in the fact that a tablet has to be taken daily, which means a comparativel high intake of hormones. This gives rise to undesirable side-effects, for example vomiting, increase in weight and so forth.

The present invention is based on the discovery of a new method of contraception in which a combination of a gestagen, in a comparatively small dose, and a depot-oestrogen is administered after the 10th day, preferably in the second half, of the menstruation cycle.

Accordingly, the present invention provides a contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises a

depot oestrogen and a comparatively small concentration of a gestagen.

The cohtraceptive preparations of the present invention may be administered, preferably in the form of oily solutions, parenterally, preferably intramuscularly or subcutaneously. However, it is also possible to administer the preparations by implantation.

It is further possible to administer the depot oestrogen and the gestagen singly, for example the gestagen orally and the oestrogen parenterally or by implantation. Accordingly, the present invention also provides a contraceptive preparation which is made up in two parts ready for administration, the one part comprising a diluent and a unit dose of a depot oestrogen and the other part comprising a diluent and approximately 0.5 to 100 mg of a gestagen.

In the new contraceptive method using the preparations of the present invention the comparatively small dose of the gestagen ensures reliable onset of withdrawal bleeding, that is to say, predictable within a span of a few days, as in natural menstruation, and the simultaneous injection of a depot-oestrogen inhibits ovulation and/or nidation in at least the following menstruation cycle by change within the female reproductive system.

Furthermore, the contraceptive action can be determined for a given period of time by appropriate variation of the concentration of active principles. When using a preparation of the present invention it is possible, by a single administration of the preparation, to prevent conception for a period covering one or more menstrual cycles, that is to say for a period of from approximately four weeks to six months or even longer, it being possibl to bring about withdrawa

bleeding within a few days after administration, without termination of the contraceptive action, by the additional parenteral or even oral administration of a gestagen.

As has already been stated, the oestrogenic and gestagenic components are preferably administered together. For this purpose the active principles are dissolved in one of the solvents known to be suitable for parenteral injection, with which a man skilled in the art will be familiar, filtered under sterile conditions and introduced into ampoules under aseptic conditions. Preference is given to oily solvents, for example sesame oil or castor oil. A diluent or a solubilizer, for example benzyl benzoate, may be added to the oil solutions to increase the solubility of the active principles.

In addition to the above-mentioned solvents, it is also possible to use vegetable oils, for example linseed oil, cottonseed oil, sunflower oil, peanut oil, olive oil and wheat oil. Also suitable are synthetic solvents, for example glycol, lactic acid esters and benzyl alcohol. Naturally, the selection of solvents given above is by no means complete. It is not necessary to provide a complete list, because a man skilled in the art will know which of the known solvents to choose for a specific purpose.

It is generally preferable to administer the contraceptive preparation at four-week intervals to imitate the regular menstrual cycle. If the interval between administratio is prolonged, for example, to several months, either on the advice of a physician or at the patient's request, only one withdrawal bleeding takes place, the complete contraceptive protection, during the interval between times of administration unless additional gestagen is given.

All substances having a prolonged oestrogenic action may be used as the oestrogen component. The period of activity should preferably be at least about 14 days. The oestrogen used is preferably administered in such doses and at such intervals that the suppression of ovulation achieved with the preparations of the present invention is at least equal to that achieved with a daily oral administration of 0.05 mg of ethynyl-oestradiol. Furthermore, the oestrogen used is preferably of the kind that produces a longer period of ovulation inhibition than orally administered ethynyl-oestradiol. Preferred oestrogen components are, in particular oestradiol esters, for example oestradiol oenanthate, oestradi undecylate, oestradiol palmitate, oestradiol butyrate and oestradiol benzoate.

The decision as to which oestrogen is the most suitable active principle to use in the preparations depends largely on the desired period of contraceptive protection. If the protective action is to cover only one menstrual cycle, in other words about four weeks, it may be quite adequate to administer oestradiol valerate, which, as is known, is liberated from a depot for only a comparatively short period.

The contraceptive preparations of the present invention suitable for parenteral administration or administration by implantation are, like the two-part preparations of the present invention, advantageously in unit dosage form. The amount of oestrogen in the unit dosage form preparations is within the range of from 0.5 to 500 mg, per unit dose. The choice of oestrogen is advantageously such that a dose of preferably 5 to 50 mg, per unit dose, is sufficient to ensure the successful use of the preparations of the present inventio

When using oestradiol oenanthate to give contraceptive protection for a period of one menstrual cycle (about four

weeks), a dose of 10 mg is generally sufficient. If the period of contraception is to be prolonged and the preferred dosage limit of 50 mg has to be exceeded, the oestrogen component may be increased to 250 mg.

Substances suitable for use as the gestagen component in the preparations of the present invention are all those which, when administered in a comparatively small dose, bring about predictable withdrawal bleeding similar in intensity and duration to normal menstruation. Preferred gestagens are those having a medium or long period of activity. The preferred concentration in the unit dosage form preparations is within the range of from 10 to 100 mg. A concentration within the range of from 0.5 to 50 mg, per unit dose, is adequate in the case of the highly active gestagens. As examples of gestagens that may be used in the preparations of the present invention there may be mentioned: progesterone and the physiologically tolerable 3-enolesters thereof, hydroxy-progesterone-caproate, hydroxy-nor-progesterone-caproate, medroxy-progesterone-acetate, nor-ethyndrone caproat and 17α-ethynyl-18-homo-19-nor-testosterone. Also suitable are 17α-hydroxy-progesterone derivatives, for example 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-

hydroxy-progesterone, 1,2-methylene-6-chloro-dehydro-17α-hydroxyprogesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol, 17α-ethynyl-Δ^{4}-oestren-17β-ol, 17α-alkyl-Δ^{4}-oestren-17β-ols and the physiologically tolerable straight-chain or branched esters thereof, for example acetates, valerates, butyrates, oenanthates and undecylates. The ester group may be substituted in the usual manner, for example, by one or more substituents selected from halogen atoms and hydroxyl, carbonyl, keto, amino and similar groups.

Having now particularly described and ascertained .....
.said invention and in what manner the same is
to be performed, declare that what claim is:

~~What we claim is:~~

1. A contraceptive preparation suitable for parenteral administration or administration by implantation, which comprises a depot oestrogen and a comparatively small concentration of a gestagen.

2. A contraceptive preparation as claimed in claim 1, which is in a form suitable for subcutaneous or intramuscular injection.

3. A contraceptive preparation as claimed in claim 1 or 2, which is in the form of an oily solution.

4. A contraceptive preparation as claimed in claim 3, containing sesame oil or castor oil as solvent.

5. A contraceptive preparation as claimed in claim 3 or 4, wherein the preparation also contains a diluent or a solubilizer.

6. A contraceptive preparation as claimed in claim 5, wherein the diluent or solubilizer is benzyl benzoate.

7. A contraceptive preparation as claimed in claim 3, containing a mixture of castor oil and benzyl benzoate as solvent.

8. A contraceptive preparation as claimed in any one of claims 1 to 7, where is in unit dosage form.

9. A contraceptive preparation as claimed in claim 8, containing 0.5 to 500 mg, per unit dose, of the depot oestrogen and approximately 0.5 to 100 mg, per unit dose, of the gestagen.

10. A contraceptive preparation as claimed in claim 8, containing 5 to 50 mg, per unit dose, of the depot oestrogen and 10 to 50 mg, per unit dose, of the gestagen.

11. A contraceptive preparation as claimed in any one of claims 1 to 10, wherein the depot oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol dibutyrate or oestradiol benzoate.

12. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is hydroxy-progesterone caproate, hydroxy-nor-progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

13. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-hydroxy-progesterone, 1,2-methylene-6-chloro-6-dehydro-17α-hydroxy-progesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol 17α-ethynyl-Δ^{4}-oestren-17β-ol or a 17α-alkyl-Δ^{4}-oestren-17β-ol or a physiologically tolerable ester thereof.

14. A contraceptive preparation as claimed in claim 13, wherein the ester is an acetate, valerate, butyrate, caproate, oenanthate or undecylate.

15. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is progesterone or a physiologically tolerable 3-enolester thereof.

16. A contraceptive preparation as claimed in any one of claims 1 to 11, wherein the gestagen is 17α-ethynyl-18-homo-19-nor-testosterone.

17. A contraceptive preparation which is made up in two parts ready for administration, the one part comprising a diluent and a unit dose of a depot oestrogen and the other part comprising a diluent and approximately 0.5 to 100 mg of a gestagen.

18. A contraceptive preparation as claimed in claim 17, wherein the part comprising a depot oestrogen is in a form suitable for parenteral administration.

19. A contraceptive preparation as claimed in claim 18, wherein the part comprising a depot oestrogen is in a form suitable for subcutaneous or intramuscular injection.

20. A contraceptive preparation as claimed in claim 17, wherein the part comprising a depot oestrogen is in a form suitable for administration by implantation.

21. A contraceptive preparation as claimed in any one of claims 17 to 20, wherein the part comprising a gestagen is in a form suitable for oral administration.

22. A contraceptive preparation as claimed in any one of claims 17 to 21, wherein one of or each of the parts is in the form of an oily solution.

23. A contraceptive preparation as claimed in claim 22 wherein the oily solution contains sesame oil or castor oil as solvent.

24. A contraceptive preparation as claimed in claim 23 wherein the oily solution also contains benzyl benzoate.

25. A contraceptive preparation as claimed in any one of claims 17 to 24, containing 10 to 50 mg of the gestagen.

26. A contraceptive preparation as claimed in any one of claims 17 to 25, containing 0.5 to 500 mg of the depot oestrogen.

27. A contraceptive preparation as claimed in any one of claims 17 to 25, containing 5 to 50 mg of the depot oestro

28. A contraceptive preparation as claimed in any one of claims 17 to 27, wh rein the depot oestrogen is oestradiol oenanthate, oestradiol undecylate, oestradiol palmitate, oestradiol dibutyrate or oestradiol benzoate..

29. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is hydroxy-progesterone caproate, hydroxy-nor-progesterone caproate, medroxy-progesterone acetate or nor-ethyndrone caproate.

30. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is 17α-hydroxy-19-nor-progesterone, 6α-methyl-17α-hydroxy-progesterone, 6-methyl-6-dehydro-17α-hydroxy-progesterone, 6-chloro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16α-methyl-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6-fluoro-6-dehydro-16β-methyl-17α-hydroxy-progesterone, 6,16-dimethyl-6-dehydro-17α-hydroxy-progesterone, 6-methyl-6-dehydro-16-methylene-17α-hydroxy-progesterone, 6-chloro-6-dehydro-16-methylene-17α-hydroxy-progesterone, 1,2-methylene-6-chloro-6-dehydro-17α-hydroxy-progesterone, 1,2-methylene-6-fluoro-6-dehydro-17α-hydroxy-progesterone, 17α-ethynyl-testosterone, 17α-ethynyl-19-nor-testosterone, 17α-ethynyl-$\Delta^{5(10)}$-oestren-17β-ol-3-one, 17α-methyl-19-nor-testosterone, 17α-ethynyl-Δ^{4}-oestrene-3β,17β-diol, 17α-ethynyl-Δ^{4}-oestren-17β-ol or a 17α-alkyl-Δ^{4}-oestren-17β-ol or a physiologically tolerable ester thereof.

31. A contraceptive preparation as claimed in claim 30, wherein the ester is an acetate, valerate, butyrat , caproate, oenanthate or undecylate.

32. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is progesterone or a

physiologically tolerable 3-enolester thereof.

33. A contraceptive preparation as claimed in any one of claims 17 to 28, wherein the gestagen is 17α-ethynyl-18-homo-19-nor-testosterone.

34. A contraceptive preparation, substantially as described herein.

DATED this 15th day of FEBRUARY, 1968.

PATENT ATTORNEY.

MDP/ME